Claims

1. A method for monitoring the expression level of a gene in a host cell by modulating the activity of a regulatory biomolecule, comprising the steps of:

(a) transforming a cell expressing a regulatory biomolecule with a nucleic acid molecule comprising an open reading frame encoding an interaction partner of said biomolecule in expressible form, wherein

(i.) said regulatory biomolecule is either a nucleic acid binding molecule that effects its regulatory activity upon binding or an allosterically controlled ribonucleic acid molecule; and

(ii.) the interaction partner of the biomolecule is encoded by a nucleic acid molecule comprising:

(1) a nucleic acid sequence encoding a tagged (poly)peptide, or

(2) a nucleic acid sequence encoding a tagged (poly)peptide or a peptide tag, a selectable marker gene and additional nucleotide sequences for site specific, in-frame integration of said nucleic acid molecule into the coding sequence of at least one host (poly)peptide of interest,

(3) a nucleic acid sequence encoding a a peptide tag, a selectable marker gene and additional nucleotide sequences for transposase-mediated, random integration of said nucleic acid molecule into the coding sequence of at least one host (poly)peptide of interest,

wherein said tag comprises the interacting residues of the interaction partner

and

(b) assessing the expression level of the gene.

2. The method of claim 1, wherein the activity or degree of modulation of the activity of the biomolecule is measured via a readout system.

3. The method of claim 2, wherein

(a) the readout system is provided by a nucleic acid molecule encoding a reporter protein;

(b) the regulatory biomolecule is

(i.) a nucleic acid binding (poly)peptide selected from the group consisting of regulators of transcription, regulators of translation, recombinases, (poly)peptides involved in RNA transport,

(ii.) an RNA molecule selected from the groups consisting of allosteric ribozymes, riboswitches or translation-regulating aptamers,

and

(c) the nucleic acid binding biomolecule is allosterically regulated.

4. The method of claim 2 or 3 wherein the nucleic acid binding (poly)peptide comprises the (poly)peptide sequence of

(a) Tetracycline repressor;

(b) Lac repressor;

(c) Xylose repressor;

(d) AraC protein

(e) TetR-based T-Rex system;

(f) Erythromycin-specific repressor MphR(A);

(g) Pip (pristinamycin interacting protein);

(h) ScbR of *Streptomyces coelicolor*;

(i) TraR of *Agrobacterium tumefaciens*; fused to the eukaryotic activation domain p65 of NFκB;

(j) chimeric proteins consisting of the:

(i.) Gal4 DNA-binding domain and either a full-length PhyA protein (PhyA-GBD) or the N-terminal photosensory domain of PhyB [PhyB(NT)-GBD] of *Arabidopsis thaliana*;

(ii.) a steroid hormone regulated system consisting of (1) a Gal4 DNA-binding domain fused to a human progesterone receptor

ligand binding domain and an NFκB-derived p65 eukaryotic transcription activation domain and (2) the inducer mifepristone

(iii.) a dimerizer system consisting of (1) a ZFHD1 DNA-binding domain fused to FKBP 12, (2) FRAP fused to the NFκB-derived p65 activation domain and (3) rapamycin, AP22565 or AP12967 as heterodimer-forming agents, or

(iv.) an Ecdysone-Inducible Expression System containing (1) a modified form of the *Drosophila* ecdysone receptor (VgEcR) fused to a VP16 activation domain, (2) the mammalian homologue RXR of *ultraspiracle*, the natural binding partner of the ecdysone receptor in *Drosophila* and (3) the inducers ponasterone A and muristerone A.

5. The method of claim 3 or 4, wherein the reporter protein of the readout system is β-galactosidase, CAT, β-glucuronidase, β-xylosidase, XylE (catechol dioxygenase), TreA (trehalase), GFP and variants CFP, YFP, EGFP, GFP+ , bacterial luciferase (*luxAB*), *Photinus* luciferase, *Renilla* luciferase, coral-derived photoproteins including DsRed, HcRed, AmCyan, ZsGreen, ZsYellow, AsRed, alkaline phosphatase or secreted alkaline phosphatase.

6. The method of claim 3 or 4, wherein the reporter protein is a protein that confers resistance to an antibiotic.

7. The method of any one of claims 1 to 6, wherein the cell is selected from a mammalian, insect, nematode, plant, yeast, protist cell, Gram-positive or Gram-negative bacteria, archaebacteria or protozoa.

8. The method of any one of claims 1 to 7, wherein all or a subset of the proteins encoded by the cell are tagged.

9. A method of producing and/or selecting a compound capable of modulating the activity of a nucleic acid binding protein comprising the steps of:

(a) conducting a selection of compounds with the nucleic acid binding target protein under conditions allowing an interaction of the compound and the nucleic acid binding protein;

(b) removing unspecificly bound compounds;

(c) detecting specific binding of compounds to the nucleic acid binding target protein;

(d) expressing in a cell, the nucleic acid binding protein and providing in trans the coding sequence of at least one indicator gene, wherein said coding sequence is under control of the target sequence of the nucleic acid binding protein;

(e) adding a candidate compound to the cell of step (d);

(f) determining the amount or activity of the indicator protein, wherein a reduced or increased amount of indicator protein is indicative of compounds, capable of modulating the activity of the nucleic acid binding protein; and

(g) selecting compounds capable of modulating the activity of the nucleic acid binding protein.

10. A nucleic acid molecule encoding a (poly)peptide comprising the sequence

(a) Met – Trp – Thr – Trp – Asn – Ala – Tyr – Ala – Phe – Ala – Ala – Pro – Ser – Gly – Gly – Gly – Ser (SEQ ID NO: 1);

(b) Trp – Thr – Trp – Asn – Ala – Tyr – Ala – Phe – Ala – Ala – Pro – Ser – Gly – Gly – Gly – Ser (SEQ ID NO: 2);

(c) Trp – Thr – Trp – Asn – Ala – Tyr – Ala – Phe – Ala – Ala – Pro – Ser (SEQ ID NO: 3);

(d) Ser – Gly – Gly – Ala - Trp – Thr – Trp – Asn – Ala – Tyr – Ala – Phe – Ala – Ala – Pro – Ser – Gly – Gly – Gly – Ser (SEQ ID NO: 4);

(e) Ser – Gly – Gly – Ala - Trp – Thr – Trp – Asn – Ala – Tyr – Ala – Phe – Ala – Ala – Ala – Ser – Gly – Gly – Gly – Ser (SEQ ID NO: 5);

(f) Ser – Gly – Gly – Ala - Trp – Thr – Trp – Asn – Ala – Tyr – Ala – Phe – Ala – Ala – Pro – Ala – Gly – Gly – Gly – Ser (SEQ ID NO: 6);

(g) Ser – Gly – Gly – Ala - Trp – Thr – Trp – Asn – Ala – Tyr – Ala – Phe – Ala – Ala – Pro – Ser – Gly – Arg – Gly – Ser (SEQ ID NO: 7);

(h) Ser – Gly – Gly – Ala - Trp – Thr – Trp – Asn – Ala – Tyr – Ala – Phe – Ala – Ala – Pro – Ser – Asp – Gly – Gly – Leu (SEQ ID NO: 8);

(i) Ser – Gly – Gly – Ala - Trp – Thr – Trp – Asn – Ala – Tyr – Ala – Phe – Ala – Ala – Pro – Ser – Gly – Glu – Gly – Ser (SEQ ID NO: 9);

(j) Ser – Gly – Gly – Ala - Trp – Thr – Trp – Asn – Ala – Tyr – Ala – Phe – Ala – Ala – Pro – Ser – Gly – Gly – Gly – Trp (SEQ ID NO: 10);

(k) Ser – Gly – Gly – Ala - Trp – Thr – Trp – Asn – Ala – Tyr – Ala – Phe – Ala – Ala – Pro – Ser – Gly – Gly – Cys – Ser (SEQ ID NO: 11);

(l) Ser – Gly – Gly – Ala - Trp – Thr – Trp – Asn – Ala – Tyr – Ala – Phe – Ala – Ala – Pro – Ser – Gly – Gly – Asp – Ser (SEQ ID NO: 12);

(m) Ser – Gly – Gly – Ala - Trp – Thr – Trp – Asn – Ala – Tyr – Ala – Phe – Ala – Ala – Pro – Ser – Gly – Gly – Arg – Ser (SEQ ID NO: 13);

(n) Ser – Gly – Gly – Ala - Trp – Thr – Trp – Asn – Ala – Phe – Ala – Phe – Ala – Ala – Pro – Ser – Gly – Gly – Gly – Ser (SEQ ID NO: 14);

(o) Ala – Val – Ser – Tyr – Thr - His – Leu – Gly – Gly – Ala – Gly –Gly – Ala – Trp – Thr – Trp – Asn – Ala – Tyr – Ala – Phe – Ala – Ala – Pro – Ser – Gly – Gly – Gly –Ser (SEQ ID NO: 15);

(p) Ala – Val – Ser – Tyr – Thr - His – Leu – Ser – Gly – Gly – Ala – Gly – Gly – Ala – Trp – Thr – Trp – Asn – Ala – Tyr – Ala – Phe – Ala – Ala – Pro – Ser – Gly – Gly – Gly –Ser (SEQ ID NO: 16);

(q) Leu – Ser – Leu – Ile – His – Ile – Ser – Gly – Gly – Ala – Ser – Gly – Gly – Ala – Trp – Thr – Trp – Asn – Ala – Tyr – Ala – Phe – Ala – Ala – Pro – Ser – Gly – Gly – Gly –Ser (SEQ ID NO: 17); or

(r) a nucleic acid molecule, the complementary strand of which hybridizes under stringent conditions to the nucleic acid molecule of any one of (a) to (q), wherein said nucleic acid molecule encodes an interaction partner which is capable of modulating the activity of a nucleic acid binding protein.

11. A (poly)peptide encoded by the nucleic acid sequence of claim 10.

12. An expression vector, comprising an expression control sequence, a multiple cloning site for inserting a gene of interest and the nucleic acid molecule of

claim 10, wherein the gene of interest is inserted in-frame with the ORF encoding the peptide.

13. A host cell containing the nucleic acid molecule or the expression vector of claim 12.

14. The host cell of claim 13, wherein the nucleic acid molecule is fused in frame to at least one chromosomal sequence encoding a (poly)peptide.

15. The host cell of claim 13 or 14, also containing

(a) the coding sequence of a reporter protein which is under control of a nucleic acid binding protein; and

(b) the coding sequence of the nucleic acid binding protein of (a),

wherein said coding sequences are operatively linked to expression control sequences.

16. The host cell of any one of claims 13 to 15, wherein the nucleic acid binding protein is a repressor of transcription.

17. The host cell of claim 16, wherein the nucleic acid binding protein is a (poly)peptide comprising the (poly)peptide sequence of

(a) Tetracycline repressor;

(b) Lac repressor.

(c) Xylose repressor;

(d) AraC protein

(e) TetR-based T-Rex system;

(f) Erythromycin-specific repressor MphR(A);

(g) Pip (pristinamycin interacting protein);

(h) ScbR of *Streptomyces coelicolor*;

(i) TraR of *Agrobacterium tumefaciens* fused to the eukaryotic activation domain p65 of NFκB; or

(j) chimeric proteins consisting of the:

(i.) Gal4 DNA-binding domain and either (1) a full-length PhyA protein (PhyA-GBD) or (2) the N-terminal photosensory domain of PhyB [PhyB(NT)-GBD] of *Arabidopsis thaliana*;

(ii.) a steroid hormone regulated system consisting of (1) a Gal4 DNA-binding domain fused to a human progesterone receptor ligand binding domain and an NFκB-derived p65 eukaryotic transcription activation domain and (2) the inducer mifepristone;

(iii.) a dimerizer system consisting of (1) a ZFHD1 DNA-binding domain fused to FKBP 12, (2) FRAP fused to the NFκB-derived p65 activation domain and (3) rapamycin, AP22565 or AP12967 as heterodimer-forming agents;

(iv.) an Ecdysone-Inducible Expression System containing (1) a modified form of the *Drosophila* ecdysone receptor (VgEcR) fused to a VP16 activation domain, (2) the mammalian homologue RXR of *ultraspiracle*, the natural binding partner of the ecdysone receptor in *Drosophila* and (3) the inducers ponasterone A and muristerone A.

18. The host cell of any one of claims 15 to 17, wherein the nucleic acid binding protein is an enhancer or activator of transcription.

19. An ensemble of host cells of any one of claims 13 to 18, wherein said ensemble comprises two or more cells, each of which contain at least one nucleic acid molecule fused in frame to an open reading frame encoding a (poly)peptide.

20. The ensemble of host cells of claim 19, wherein said ensemble contains subpopulations with different open reading frames being fused to said nucleic acid molecule.

21. The ensemble of host cells of claim 20, wherein the sum of said open reading frames forms the proteome of the host cell.

22. A non-human animal comprising the host cell of any one of claims 13 to 18 or the ensemble of any one of claims 19 to 21.

23. A kit comprising

(a) the nucleic acid molecule of claim 10;

(b) the (poly)peptide of claim 11;

(c) the vector of claim 12;

(d) the host cell or ensemble of host cells of any one of claims 13 to 22; and/or

(e) instructions for use;

in one or more containers.

24. Use of the (poly)peptide of claim 11, the nucleic acid molecule of claim 10, the expression vector of claim 12 or the host cell or ensemble of host cells of any one of claims 13 to 22 for monitoring expression of a gene.